New drug target for X-linked lymphoproliferative disease identified

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An international team of scientists including researchers at St. Jude Children's Research Hospital have identified a crucial signaling enzyme as a possible therapeutic target for the treatment of a heritable immune disease. X-linked lymphoproliferative disease is a life-threatening condition that has few treatment options. Affected individuals are vulnerable to massive accumulation and activation of white blood cells known as T cells should they become infected with Epstein-Barr virus, the virus that causes infectious mononucleosis. Without treatment, this accumulation of activated T cells leads to severe organ damage and, in many cases, death. The study appears online in the January 13 issue of *Science Translational Medicine*.

Scientists have known for some time that X-linked lymphoproliferative disease is a heritable disorder caused by germline mutations in the SH2D1A gene. When this gene is affected it leads to defects in a specific adaptor molecule known as SAP (Signaling Lymphocytic Activation Molecule-associated protein) that plays important roles in the signaling events related to receptors on the surface of T cells. Without an effective SAP adaptor molecule, normal cell death processes (apoptosis) are impaired and an enzyme known as diacylglycerol kinase alpha is activated. This team questioned whether the over-activation of diacylglycerol kinase alpha might contribute to the reduced apoptosis of X-linked lymphoproliferative disease T cells and the accumulation of T cells that occurs following infection with Epstein-Barr virus.

The researchers showed that inhibition of diacylglycerol kinase alpha

using specific drugs restored the sensitivity of X-linked lymphoproliferative T cells to cell death. The scientists observed similar results when they looked at the effects of "knocking out" the same enzyme in cultured X-linked lymphoproliferative T cells using inhibitory RNA molecules. Consistent with these observations, pharmacologic inhibition of diacylglycerol kinase alpha also curtailed the expansion of T cells in virus-infected mice that serve as a model organism to study X-linked lymphoproliferative disease.

"Patients with X-linked lymphoproliferative disease are prone to severe Epstein-Barr virus infection due to a weakened immune system," said Kim Nichols, a member of the St. Jude Department of Oncology and one of the lead authors of the study. Dr. Nichols identified the SH2D1A gene in 1998 and her laboratory has been studying how SAP regulates immune cell development and function for over 15 years. "Infection with Epstein-Barr virus can have potentially fatal consequences for these patients." She added: "This severe disease is a double-edged sword. On the one hand the immune system is significantly weakened. However, detrimental side effects occur due to the expansion and hyper-activation of T cells. Together with our collaborators in Europe and other institutions in the United States, we wanted to establish the biochemical mechanism underlying these changes so that we could develop better treatments for X-linked lymphoproliferative disease patients experiencing hyper-inflammation."

"Our findings suggest that inhibition of diacylglycerol kinase alpha could reverse some of the life-threatening effects linked to Epstein-Barr virus infection of patients with X-linked lymphoproliferative disease," said Nichols.

T cells from patients with X-linked lymphoproliferative disease are hard to obtain in sufficient quantities to permit many experiments and such experiments in the laboratory do not fully recapitulate the manifestations

that are seen in patients. The St. Jude researchers therefore turned to a model system that replicates the conditions of the disease in genetically modified mice. Mice deficient in SAP, when challenged with lymphocytic choriomeningitis virus, show similar symptoms to patients with X-linked lymphoproliferative disease, including an abnormal accumulation and activation of T cells. Collectively the data from cultured human T cells and SAP-deficient mice show that inhibition of diacylglycerol kinase alpha had beneficial effects on restoring the natural balance of the immune system.

"These results are very exciting and provide proof of principle that treatment with an inhibitor of diacylglycerol kinase alpha could help patients with the symptoms experienced after Epstein-Barr virus infection. However, this work is still at an early preclinical stage of investigation. We have identified a new target for X-linked lymphoproliferative disease but further work is needed to identify and advance the best drug candidate from preclinical testing to a viable treatment option for patients."

More information: "Inhibition of diacylglycerol kinase α restores restimulation-induced cell death and reduces immunopathology in XLP-1," DOI: 10.1126/scitranslmed.aad1565

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